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IMMUNISATION AND GASTRIC COLONISATION WITH *HELICOBACTER FELIS*

Keith Heap and Adrian Lee

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Introduction

There is accumulating evidence that long term infection with *Helicobacter pylori* is a prerequisite for the development of atrophic gastritis and the subsequent development of gastric cancer in a subset of persons in certain developing countries. Thus, introduction of intervention strategies at an early age may influence the morbidity and mortality of this serious disease. Immunisation would be an attractive option but, given *H. pylori* can survive in the body for tens of years in the presence of a strong immune response, may not be effective. *Helicobacter felis* will colonise the gastric mucosa of SPF mice in large numbers occupying the gastric pits and mucus. Like *H. pylori* in humans this bacterium will remain for the life of the animal. Thus, the *H. felis*- infected mouse would appear to be a good model to test the hypothesis that immunisation can protect against colonisation with gastric helicobacters.

Methods

SPF mice were immunised by intravenous injection of 0.1 ml of a suspension of viable *H. felis* (10^8 / ml) once a week for 5 weeks or infected *per os* over 5 days with three doses of the bacterium. Immune responses of both these groups of animals were measured. A similar group of parenterally immunised animals were challenged with living cultures of *H. felis*. A final group of orally *H. felis* -infected animals was cleared of the organism with triple anti-microbial therapy for 28 days (tetracycline, metronidazole, bismuth subcitrate). These animals and controls that had been given saline instead of triple therapy were then challenged with a living culture of *H. felis*. All challenged animals were assessed for *H. felis* colonisation by rapid urease testing of gastric tissue and histology.

Results

Parenteral immunisation of mice with living cultures of *H. felis* induced a very high level of serum IgG, significant IgM and IgA could be detected in the bile. Serum responses post oral infection were much less and developed slowly. Hyperimmunisation of mice with an intravenous injection of a live culture of *H. felis* had no protective effect on gastric colonisation. In contrast, in mice cleared of infection with *H. felis* by administration of a one month treatment of antibiotics, some effect on rechallenge was seen. Colonisation was significantly delayed, with numbers of animals showing no urease reactivity for up to 10 days after rechallenge with an inoculum of *H. felis* that always gave 100% positivity in normal animals.

Conclusion

Parenteral immunisation with *H. felis* gave absolutely no protection against gastric colonisation. The same is likely to be true for *H. pylori*. However, preliminary experiments show that previous oral infection with living bacteria did appear to have some effect on reinfection. Further experiments are in progress to assess the value of oral immunisation against infection with gastric helicobacters.

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Demonstration of a Cytotoxin from *Campylobacter pylori*

V. Hupertz*, S. Czinn

In order to determine if *Campylobacter pylori* produces a cytotoxin, a study was performed using bacterial lysates from three clinical isolates of the organism. The lysates were cytotoxic for Chinese hamster ovary cells, as determined by a microtiter assay. The lysates were also lethal for mice after intraperitoneal injection. Loss of toxicity and lethality followed trypsinization, heating and acidification of cell-free lysates. It is concluded that the toxic factor(s) in *Campylobacter pylori* may be a protein.

Gastroduodenal disease is a common and costly disease in industrialized nations. Since back-diffusion of hydrogen ions is considered by many to be the primary cause of gastric mucosal damage, therapy has been directed at inhibiting gastric acid secretion. However, the relapse rate has remained extremely high, sometimes approaching 100% despite standard therapeutic regimens, which suggests another etiology for this illness (1). The recovery of *Campylobacter pylori* from gastric biopsies of patients with histologic evidence of gastritis or gastric and duodenal ulcers has provided a basis for presumption of a bacterial etiology in some forms of gastroduodenal disease (2–4). Biopsy material from *Campylobacter pylori*-infected patients has demonstrated marked epithelial disruption of the gastric mucosa and a significant inflammatory response within the lamina propria.

The goal of this study was to determine if *Campylobacter pylori* produces a cytotoxin. The presence of a bacterial-associated toxin was evaluated in both an animal model and a cytotoxin microtiter assay.

Materials and Methods. The three bacterial strains of *Campylobacter pylori* studied included one clinical isolate each from a pediatric and adult patient with gastritis (P1.2 and A3, respectively) and a strain graciously supplied by Dr. M. A. Karmali, Hospital for Sick Children, Toronto, Canada. The identity of the test strains was confirmed by Gram stain, colony morphology, urease, catalase and oxidase production. For the mouse virulence assay, the bacteria were incubated microaerophilically at 37 °C in 10% CO_2 for four days on Columbia agar supplemented with 5% sheep blood, recovered in PBS, and harvested by centrifugation.

Chinese hamster ovary-K1 (CHO) cells (ATCC, CCL61 Rockville, MD, USA) were incubated in Hams-F12 media (Flow Laboratories, USA) supplemented with 10% fetal calf serum (FCS), 50 IU/ml of penicillin, 50 mcg/ml of streptomycin, and 2.5 mcg/ml of amphotericin at 37 °C. Incubation was performed in 5% CO_2 in 25 cm^2 tissue culture flasks. For the microtiter assays, freshly trypsinized CHO cells were counted in a Neubauer counting chamber and diluted with Hams-F-12 media to a final concentration of 5×10^4 cells/ml.

Bacterial suspensions of *Campylobacter pylori* were kept in ice and lysed by sonication using 4–30 s bursts. Cellular debris was cleared by centrifugation at 12,000 × *g* for 15 min. The resulting supernatants were filter sterilized using 0.45 μ filters. Serial dilutions were prepared in PBS for the mouse virulence assays and in Hams-F12 without FCS for the CHO microtiter assays.

Serial dilutions of bacteria in PBS or cell-free lysates were injected intraperitoneally into 6-week-old 20 g CF-1 male mice (Charles River Laboratories, USA) and survivors were counted daily for a total of four days. Control mice received PBS. The bacterial inoculum or dilution of cell-free lysate required to kill 50% of the test animals (LD50) was calculated by the method of Reed and Muench (5).

The cytotoxicity assay used was a modification of the technique described by Gentry and Dalrymple (6). CHO cells were suspended in Hams-F12 medium supplemented with 10% FCS to a final concentration of 5×10^4 cells/ml. Aliquots of 0.1 ml were placed into each well of 96 well microtiter plates (Becton Dickinson, USA). Each plate was incubated at 37 °C with 5% CO_2 for 18–24 h to allow the formation of monolayers. Excess media was removed from each well. Dilutions of cell lysates in Hams-F12 without FCS were added to each well in 0.1 ml aliquots and incubated for an additional 18–24 h. Negative controls were included on each plate. Detached cells, residual media and toxin were removed by vigorous shaking and the remaining cellular monolayers were fixed with 2% formalin in PBS for 1 min. The fixative was removed and the CHO cells were stained with 0.1% crystal violet in 5% ethanol-2% formalin-PBS for 20 min. Excess stain was removed and the plates were air dried. To quantitate loss of adherence, the stain eluted from two wells of the same toxin dilution was combined, diluted with 0.9 ml PBS, and the absorbance measured at 595 nm. Using four data points for each dilution, an elution profile was obtained by plotting the log of the toxin dilution versus the absorbance. The

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dilution that produced 50% detachment (CD50) was chosen as the endpoint.

Results and Discussion. Intraperitoneal injection with whole, live *Campylobacter pylori* P1.2 into mice resulted in death 1 to 2 days after injection. The LD50 was 1.9×10^8 CFU/mouse (Table 1). Control mice injected with PBS alone survived.

Intraperitoneal injection of sterile cell-free bacterial lysates was lethal. The LD50s were similar for the three bacterial strains studied. Strain P1.2 had an LD50 of 1.25 mg protein/mouse, strain A3 an LD50 of 1.1 mg protein/mouse, and strain 571 and LD50 of 1.85 mg protein/mouse (Table 2). Death generally occurred within 48 h of injection and the mice showed signs of illness (i.e. decreased activity, ruffling of fur and decreased food intake) 3–4 h after injection. The toxic factor present in the cell lysate was partially characterized. Treatment of the cell lysate with trypsin resulted in complete loss of lethality in the murine virulence assay. Heating the cell lysate up to 100 °C for 15 min also caused a loss of toxic activity. The stability of the toxic factor(s) to pHs ranging from 4.0 to 10.0 revealed that the toxic activity was lost at a pH < 4.5.

Using the CHO microtiter assay, cell viability was markedly diminished in the presence of cell lysate. Morphology of the cells remaining in the monolayers was maintained, consistent with a cytotoxic effect rather than a cytotonic effect. From the plot of absorbance versus log protein concentration, a CD50 of 0.16 mg protein/ml was obtained (Figure 1).

The mechanism by which *Campylobacter pylori* causes gastritis is unclear. Using the murine virulence assay, live *Campylobacter pylori* was demonstrated to be lethal. Attempts to recover the organism from the peritoneal cavity, gastric mucosa, stool and blood were unsuccessful. This suggests that the lethal effect may be due to the release of toxic factors from *Campylobacter pylori* rather than infection and sepsis. In this study we were able to demonstrate that *Campylobacter pylori* produced a substance which is cytotoxic to CHO cells grown in tissue culture. There was no evidence of a cytotonic effect as has been described for cholera toxin (7). The cytotoxic effect was reproducible and quantifiable, yielding a CD50 of 0.16 mg protein/ml. The exact mechanism responsible for these cytotoxic effects remains to be determined. The effect of the lysate after intraperitoneal injection into adult mice was also examined.

Table 1: Results of i.p. injection of *Campylobacter pylori* into 6-week-old mice. Data shown is representative of two experiments.

Inoculum (CFU)	Number of mice injected	Number of mice that died
5.2×10^8	6	6
2.5×10^8	6	5
1.0×10^8	5	0
3.8×10^7	6	0

Table 2: Results of i.p. injection of sterile *Campylobacter pylori* lysates into 6-week-old mice.

Campylobacter pylori strain	Protein concentration (mg/ml)	Number of mice injected	Number of mice that died
P1.2	4.5	11	11
	2.5	9	8
	1.5	10	10
	0.94	4	0
A3	6.4	10	9
	3.2	10	10
	1.6	10	10
	1.1	10	4
	0.64	5	2
	0.06	5	0
571	6.0	9	9
	3.0	9	5
	1.5	9	5
	1.0	9	1
	0.75	9	0

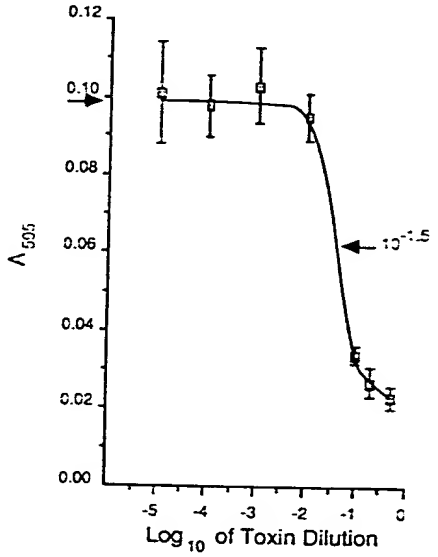

Figure 1: *Campylobacter pylori* toxin assay. The elution pattern is obtained by plotting the absorbance values ± SD at 595 nm (A_{595}) of the eluted dye against the log of the toxin dilution. The control dye absorbance (representing zero detachment) value is indicated on the ordinate. The CD50 was obtained by extrapolation from the curve. The protein concentration of the lysate prior to dilution was 2.5 mg/ml.

The lysates were found to be lethal after intraperitoneal injection and their effect was dose-dependent. This was true for the three strains of *Campylobacter pylori* tested. The LD50s were similar, requiring concentrations in the range 1.10–1.85 mg protein ml of crude lysate. Initial characterization of the toxin showed loss of activity upon trypsinization, acidification up to pH 4.0 and heating up to 100 °C for 15 min. This indicates that the toxic factor is protein in nature.

Campylobacter pylori has now been isolated from the gastric mucosa of most patients with gastroduodenal disease. Koch's postulates have been fulfilled in humans, proving that *Campylobacter pylori* is a pathogen (8, 9). We have shown that *Campylobacter pylori* is ten times more virulent than *Campylobacter jejuni* in mice (10), and that it produces a toxin that is lethal to mice and cytotoxic to CHO cells. Partial characterization suggests this toxin is protein in nature. Further studies are necessary to determine whether this toxin is responsible for the gastroduodenal disease associated with *Campylobacter pylori*.

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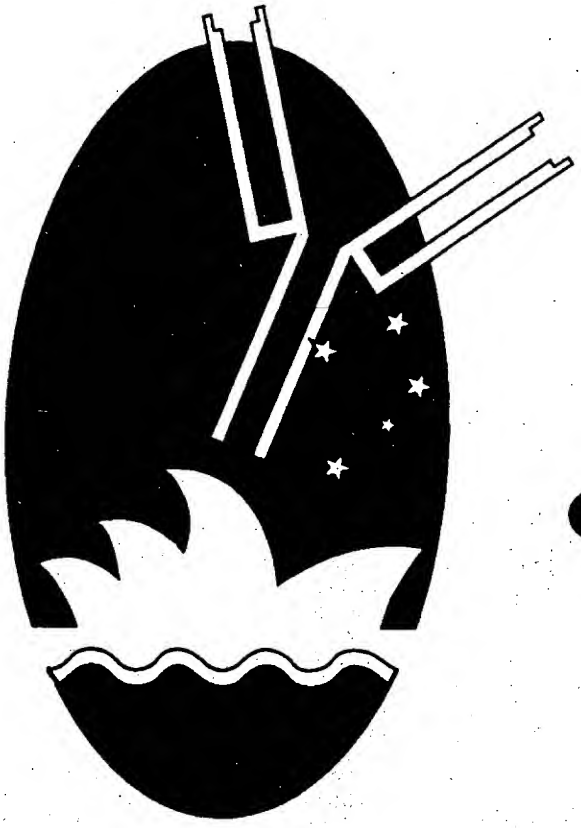

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W3.2.6

HELICOBACTER PYLORI SPECIFIC B-CELLS IN GASTRIC MUCOSA

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Aim: To determine the presence of antibody secreting cells (ASCs) with specificity for different *H. pylori* antigens in gastric mucosa of infected patients with duodenal ulcers (DU) and in asymptomatic carriers (AS). **Methods:** Ten punch biopsies were collected from antrum and corpus, respectively, of *H. pylori* infected patients with DU, asymptomatic *H. pylori* carriers and non-infected, healthy subjects. Mononuclear cells were isolated from the biopsies by enzymatic treatment and assayed for spontaneous production of antibodies with specificity for different *H. pylori* antigens, i.e. total membrane proteins (MP), flagellin, urease, LPS (strain E50) and a 30 kD protein, by the ELISPOT-assay. **Results:** All but one of the *H. pylori* infected subjects had high frequencies of ASCs, both in antrum and corpus, that reacted with flagellin. Most of them also had urease- and MP-specific ASCs. In none of the non-infected subjects, ASCs that reacted with any of the antigens tested were detected. No significant difference in antigen specificity was noted between symptomatic and asymptomatic subjects.

	Frequency of subjects with *H. pylori*-specific ASCs (≥20 ASCs/10^5 MNCs)			Mean no. of ASCs/10^5 MNCs [a]		
Antigen	DU, Hp+	AS, Hp+	Hp-	DU, Hp+	AS, Hp+	Hp-
Membrane protein	6/7	9/10	0/12	22	37	0
Flagellin	7/7	9/10	0/12	76	96	0
Urease	5/7	10/10	0/12	13	78	0
LPS E50	2/7	2/10	0/12	3	2	0
30 kD	1/7	2/10	0/12	4	3	0

[a] The values are based on results from all subjects and are mean values of the ASC frequencies in antrum and corpus.

Conclusions: *H. pylori* induces strong antibody responses locally in the stomach, especially against flagellin and urease, in symptomatic as well as in asymptomatic individuals. No detectable difference in frequencies of ASCs in antrum and corpus was observed.

W3.2.7

A MIXED TH1/TH2 RESPONSE MAY BE NECESSARY FOR EFFECTIVE IMMUNITY AGAINST *HELICOBACTER*

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Examining the type of immune response required to stimulate protective immunity against *Helicobacter* infection has produced conflicting results. Cholera toxin (CT), which is a potent stimulator of IL-4 (a Th2 type cytokine), is the adjuvant most commonly used to stimulate protection in *Helicobacter* immunisation studies. Our work with IL-4 deficient mice also indicates that this Th2 type cytokine is required to induce protective immunity against *Helicobacter* (F. Radcliff et al unpublished data). However cytokine analysis of mice immunised and protected from *H. felis* challenge suggests that IFNγ, a typical Th1 cytokine, is present whereas Th2 cytokines are undetectable (Mohammadi et al, 1996, J. Immunol). Therefore to assess the significance of IFNγ in *Helicobacter* immunisation, IFNγ receptor negative (IFNγ-/-) and wildtype IFNγ+/+ SPF 129/Sv mice were immunised on days 0, 7, 14 & 21 with *H. felis* sonicate + CT or PBS and challenged 3 weeks later with live *H. felis*. After a further 3 weeks the experiment was terminated. Our initial infection results (by urease assay) indicate that IFNγ is required for effective immunisation against *Helicobacter*. The immune response to *H. felis*, including the serum IgG response, salivary IgA response and the influence of IFNγ on post-immunisation gastritis are discussed. These data suggest that a mixed Th1/Th2 type response may be required for effective immunisation against *Helicobacter*.

W3.2.8

HELICOBACTER PYLORI CATALASE: A NOVEL ANTIGEN FOR THERAPEUTIC IMMUNISATION

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The goal of this study was to investigate the ability of therapeutic immunisation with purified recombinant *Helicobacter pylori* catalase (rCatalase) to cure infection in the *H. pylori* (Sydney strain - SS1) mouse model. SPF C57/Bl6/J mice were infected with *H. pylori* (SS1) and then therapeutically immunised, IG, five weeks later on days 1, 10, 11 & 12. Mice received either: *H. pylori* (clinical isolate) whole cell sonicate (1mg/mouse/dose) with cholera toxin (CT - 10μg); purified *H. pylori* rCatalase (~125μg) with CT; or saline alone. Twelve days after the final immunisation, half of the animals were collected and their *H. pylori* infection status determined by gastric biopsy urease assay (gastric biopsies were fixed in formalin and saliva and serum also collected for future analysis). No significant reduction in *H. pylori* infection was noted at this time. However, 32 days after the final immunisation, infection was reduced or cured in a significant proportion ($p<0.05$, Fisher Exact test) of the mice immunised with *H. pylori* sonicate plus CT (5/10) or rCatalase plus CT (5/9), as compared to 100% infection (10/10) in control animals. Thus both *H. pylori* sonicate and purified recombinant *H. pylori* catalase, when combined with the mucosal adjuvant CT, were able to significantly cure *H. pylori* infection in mice. The high infection levels 12 days post immunisation, with significantly reduced levels in the same groups 20 days later, suggests that the cure is the result of a long-term process and that later collection may reveal higher cure rates. Catalase has recently been shown by our group (F.Radcliff, *et. al.* submitted) to provide protection against *H. pylori* infection in mice, and this study now demonstrates its therapeutic value in the treatment of *H. pylori* infection.

W3.2.9

Helicobacter pylori infections in IgA deficiency: lack of role for the secretory immune system

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Secretory IgA (sIgA) is the predominant immunoglobulin class in the gastrointestinal tract and plays an important role as a first line defence against bacterial and viral antigens. IgA-deficient individuals show a higher than expected frequency and longer duration of gastrointestinal infections caused by enteric pathogens such as Giardia, Salmonella and Campylobacter. There is also a markedly increased risk for development of gastric malignancies in IgA deficient patients compared to the general population. Whether infection with *H. pylori* could be a reason for the increased incidence of gastric cancer is still unclear.
Current strategies for the development of a vaccine against the microorganism in normal carriers are concentrating on stimulation of Th2 cells in order to generate a local IgA response in the gut. Conceptually, if infection is usually cleared by the secretory immune system, IgA deficient individuals would be expected to be at high risk both for chronic infection and reinfection after successful antimicrobial therapy.
We therefore determined the prevalence of seropositivity and titer of IgG antibodies against *H. pylori* infections in 72 IgA deficient individuals and compared the result to 144 age matched normal blood donors.
There was no difference in the frequency of seropositivity, nor titer, against *H. pylori* in serum samples from IgA-deficient patients (or in a subgroup of healthy IgA deficient blood donors) and age-related normal blood donors. A subsequent study on 50 additional samples from IgA deficient patients confirmed this finding.
Thus, it appears as though lack of secretory IgA does not have a major influence on the prevalence of the infection, nor is it reflected in the severity of the disease (as judged by titers of specific IgG antibodies). These results argue against a pivotal role for IgA in the defence against Helicobacter, raises questions about current strategies for the development of an oral vaccine against *Helicobacter pylori* and may point to a need for alternative therapeutic strategies.